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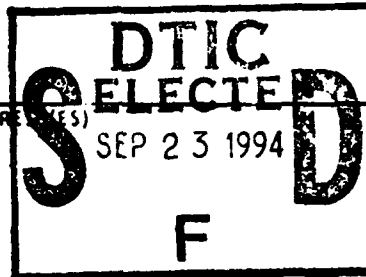
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Investigations of adaptive neural networks were conducted using the classically conditioned eyeblink of rabbit, a widely used model system for studies of learning and memory. Our work has focused on processes that mediate adaptive timing of conditioned responses, an important question in the field of learning and motor control. The following experimental projects were conducted: (a) A recording study of the medial geniculate neurons during two-tone differential trace conditioning. (c) A recording study of the ventrolateral pontine reticular formation and pontine nuclei during two-tone differential conditioning. (d) Anatomical experiments using WGA-HRP that clarify cerebellar and red nucleus circuits involved in eyeblink conditioning. (e) Behavioral experiments examining the role of temporal uncertainty in conditioned response timing and topography. (d) Behavioral experiments on asynchronous bilateral eyelid conditioning in rabbits.

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Dr. Genevieve Haddad, Ph. D., Program Manager

Biological and Theoretical Studies of Adaptive Networks: The Conditioned Response
(UMass Account 5-28286)

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I. Summary

Investigations of adaptive neural networks were conducted using the classically conditioned eyeblink of rabbit, a widely used model system for studies of learning and memory. Our work has focused on processes that mediate adaptive timing of conditioned responses, an important question in the field of learning and motor control. The following experimental projects were conducted: (a) A recording study of the medial geniculate neurons during two-tone differential *trace* conditioning (Dr. Kevin O'Connor). (c) A recording study of pontine nucleus neurons during two-tone differential conditioning (Michael Hirl). (d) Anatomical experiments using WGA-HRP designed to clarify red nucleus innervation of the cerebellum (Marcy Rosenfield). (e) Behavioral experiments examining the role of temporal uncertainty in conditioned response timing and topography (Michael Hirl, June Seek Choi) (d) Behavioral experiments on asynchronous bilateral eyelid conditioning in rabbits (June-Seek Choi). The studies listed under (a) - (e) have been reported at recent meetings of the Society for Neuroscience. The last item (d) will be presented at the 1994 meeting of the Society for Neuroscience.

In addition to the above, we initiated two lines of research that can only be completed if supported by some sponsor other than AFOSR. We are presently preparing a proposal to NIMH for such support. One of the projects initiated during the second (terminal) year of this project is a behavioral experiment designed to test predictions of the Desmond-Moore 1988 computational model of conditioning. We refer to this model by the acronym VET, for learning associative *values* based on *expectations* about *timing*. This project involved new graduate student Darlene Brunzell. The second new initiative involves single-unit recording from the cerebellum of awake, behaving rabbits in order to determine how information about the timing of the US is represented in the firing patterns of single neurons. Our strategy is to use a technique we refer as conditioning under temporal uncertainty, described later on, in order to create complex CR topographies. To date, there is virtually no information about how single neurons encode information that gives rise to complex CR topographies such as those with multiple amplitude peaks. This report does not present results of these newly initiated studies, because no firm conclusions are possible at this time.

Besides the experimental work, we completed a major upgrading of experimental facilities with funds provided with this award. All of the software for automatic control of experiments and data

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acquisition were developed here. Two laboratories for single-unit recording in awake, behaving animals were constructed. Another laboratory contains a computer-controlled setup for behavioral experiments (i.e., no neuronal recording involved) that permit simultaneous recording from two eyes of as many as eight animals. The behavioral lab went on line in June 1993. The two-eye eyeblink transducers were developed and manufactured at Yale University and purchased with funds from this award. These new laboratories will enable us to continue research relevant to adaptive networks, provided an alterative sponsor can be found.

II. Research Objectives

The general objectives for the reporting period were the same as those stated in previous reports going back to those submitted in connection with AFOSR Grants 83-0215, 86-0182, and 89-0391. These goals and our approaches to them remain unchanged, so only a brief summary is presented here.

Basically, we use the classically conditioned eye blink as a model system for theoretically oriented behavioral and neurophysiological studies of learning. At the behavioral level, we have conducted and published several articles testing specific prediction from computational models regarding basic phenomena of classical conditioning. Our computational models allow for precise predictions about the timing and topography of conditioned responses in a variety of paradigms. In this regard we have have been recognized leaders in the field. These efforts continue to be a central focus in our research. At the neurophysiological level, we have conducted and published several reports of single-unit activity in awake behaving rabbits. Brain regions that have been targeted in these studies include the cerebellum, the red nucleus, brainstem reticular formation, and the medial geniculate nuclei of the thalamus. As an adjunct to the recording work, we have elaborated the efferent projections of the red nucleus and the afferent projections of the portion of cerebellar cortex involved in the conditioned eyeblink, using fiber-tracing methods derived from peroxidase histochemistry.

III. Status of Research

The easiest way to describe the status of the research is to summarize the main research efforts of each individual working on this project and under my general direction.

1. Dr. Kevin O'Connor has completed a study of MGN neuronal activity during trace conditioning. This study recorded from neurons in three divisions of the MGN—dorsal (dMGN), medial (mMGN), and ventral (vMGN). In agreement with earlier studies using multiple-unit recording, most mMGN cells respond to a reinforced conditioned stimulus (CS+) with a short-latency and short-duration increase in firing rate. This increase exceeds the firing triggered by the non-reinforced CS-. In addition, firing rates to CSs are greater on trials with conditioned responses than trials without conditioned responses. Some MGN cells (roughly 25 per cent) are inhibited by CS+ and this inhibition exceeds that observed to CS-. Cells of mMGN showing primary excitation or inhibition to CS onsets were excitatory with respect to CS offset. This observation is of theoretical interest because the VET model postulates the existence of stimulus offset processes that mediate the timing and form of conditioned responses. An eleven page account of this study was appended

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to last year's annual technical report. Although Dr. O'Connor is in the process of moving to UC Davis for a new position, we hope to complete a full manuscript reporting this work within the next few months, if not weeks.

2. Graduate student Michael Hirl built the new behavioral lab under the guidance of O'Connor and myself and with consultation from local electronics experts. Hirl also concluded a study of single-unit activity in the dorsolateral pontine nucleus which was designed to determine whether the stimulus trace processes assumed by the VET model are expressed in this structure. Unlike the MGN, no such process was evident.

As indicated in my six-month progress report (Feb 25, 1993), Hirl switched his efforts to studies of *conditioning under temporal uncertainty*. This is a new area of empirical research designed to challenge computational models of conditioned responding and to establish new benchmarks for neural approaches. In two experiments, rabbits were trained with randomly varying CS-US intervals (ISIs) with a mean ISI of 500 ms. The CS was a 300-ms 1-kHz 80-dB tone, and the US was a 2.5-mA 1-ms dc pulse to the periocular tissue of the right eye. There were 100 trials/session at a rate of 3/min, with every 10th trial a CS-alone probe. Independent variables were W, the range of possible ISIs in milliseconds, and m, the number of possible ISIs within W. Dependent variables included CR latency (L), time of peak CR amplitude (P), and movement time ($MT = P - L$).

In Experiment 1, $W = 0, 50, 100, 200$, and 400. For $W = 0$, $m = 1$; for $W \geq 50$, $m = W/2$. Each of 4 animals experienced all Ws. There were 12 sessions under the initial W ($W = 0$ or 400) and 10 for each subsequent W. The results from the last 5 sessions/W were: (a) probe-trial CR topographies spanned W; (b) MT was constant for $W = 0$ and 50 but increased linearly with W for $W \geq 100$, with P increasingly overshooting the mean ISI of 500 ms; (c) Pearson correlation coefficients between L and P, computed for each animal from probe trials, averaged .25 and were unrelated to W.

In Experiment 2, $W = 400$ and $m = 2, 3, 4$, or 5 for different animals. Probe-trial CR topographies after 20 sessions spanned W. They were bimodal for $m = 2$ (ISIs 300 and 700) but unimodal for $m = 3-5$, and P was an inverted-U function of m. On CS-US trials, CRs began to return to baseline immediately upon the occurrence of the US, suggesting it had become a conditioned inhibitor, as predicted by the VET model. Experiment 2 has been replicated by NSB graduate students June-Seek Choi and Darlene Brunzell.

The results of experiments on conditioning under temporal uncertainty were presented at the 1993 meetings of the Society for Neuroscience. They were also the basis of a presentation by me at the Annual New England Conference on Sequencing and Timing held here March 12, 1994. Publication is planned.

3. Technician Marcy E. Rosenfield has been investigating brain stem and cerebellar circuits involved in the conditioned NMR using implanted WGA-HRP as a marker. The main new finding is the existence of a direct projection from the red nucleus to a portion of the cerebellar cortex known as Larsell's HVI, which is homologous to the simplex lobe in the cat. This part of the cerebellar cortex has been implicated in the generation of the classically conditioned eye blink/NMR. The motor program for the conditioned response is presumably learned by the cerebellum and relayed to motoneurons via the red nucleus. Projections from the red nucleus to HVI could be important

for brain stem and cerebellar processes involved in classical conditioning (e.g., Moore, J. et al, *Biol Cyber*, 62:17, 1989).

Rosenfield implanted WGA-HRP (Sigma L3892) unilaterally into HVI of albino rabbits (Mori et al, *Brain Res. Bull.*, 6:19, 1981). The pipette remained *in situ* for 45 hours before sacrifice. Animals were perfused transcardially (descending aorta clamped) with approximately 2 L of .9% saline followed by .5 L of 10% formalin and then 3 L of 12% sucrose solution at 4 degrees C. Brains were blocked immediately on extraction (saving only the brain stem and cerebellum), placed in 30% sucrose in .1 M phosphate buffer (pH = 7.2), and stored at 4 degrees C for 20 h. The cerebellum was embedded in gelatin. Frozen sections were cut transversely at 60 μ , mounted on subbed slides, and reacted with TMB. Implantations met our criterion for inclusion if (a) diffusion did not involve cerebellar deep nuclei; (b) retrogradely labeled neurons were seen in the pontine nuclei, spinal trigeminal nucleus par oralis, and the dorsal accessory olivary nucleus.

Nine criterion cases showed an average of 21 retrogradely labeled cells in contralateral red nucleus at the level of the 3rd nerve within subregions implicated in eyeblink conditioning by lesioning (Rosenfield & Moore, *Behav. Brain Res.*, 10:393, 1983) and recording (Desmond & Moore *Neurosci. Res.*, 10:260, 1991) studies. These observations are consistent with previous reports (Dietrichs & Walberg, *Exp. Brain Res.*, 50:353, 1983; Rosenfield & Moore, *Soc. Neurosci. Abstr.*, 17:870, 1991) and also with the hypothesis that learning in the red nucleus may be a precursor to learning in the cerebellum.

We hope to have a complete manuscript describing this work within the next 12 months. The main results are summarized in a series of figures appended to this report.

4. Graduate student June Seek Choi conducted an experiment on asynchronous bilateral eyeblink conditioning in the rabbit in order to develop a model system for learned coordinated action. In unilateral eyelid conditioning, a CS is followed at some fixed time by a US applied to one eye. Conditioned eyelid movements develop in both the ipsilateral (stimulated) eye and in the contralateral eye. Although reduced in amplitude and prone to extinction, the timing of the contralateral response matches that of the trained eye (Stickney, KJ & Donahoe, JW, *Animal Learning & Behavior* 1983, 11: 60-66).

Choi instilled asynchronous timing of conditioned eyelid movements using a procedure in which the CS preceded asynchronous USs applied to the right and left eyes *on the same trial*. Three albino rabbits received 100 trials/daily session, with an intertrial interval of 20 s. Ten of these trials were CS-alone probes. The CS was an 80-dB 1-kHz tone of 300-ms duration. The right and left USs were 2.5-mA 1-ms dc pulses delivered via stainless steel sutures. The right-eye CS-US interval was 300 ms. The animals were first trained for 10 sessions with a temporal separation between the right-eye and left-eye USs of 300 ms. Although the responses of the two eyes were initially coupled, training results in a temporal separation between the two responses that matched the separation of the two USs. The temporal separation between the two USs was then reduced progressively by shortening the left-eye CS-US interval in stages consisting of 10 sessions each. The first reduction was to 154 ms, followed by separations of 79 ms, 42 ms, 23 ms, and finally 10 ms.

The timing of the left-eye conditioned response progressively decreased to match whatever left-eye CS-US was then in effect. The timing of the right-eye conditioned responses remained invariant, matching its 300-ms CS-US interval. Thus, the timing of right and left conditioned responses de-

pendent only on their respective CS-US intervals.

These results are important because they indicate that it is possible to uncouple bilateral learned responses that are normally synchronized. Furthermore, there appears to be no temporal separation between asynchronous USs that cannot be resolved into an equal separation in the timing of the two effectors. This study will be presented at the next meetings of the Society for Neuroscience.

IV. Technical Reports

1. Moore, J. W. Knowledge structures in temporally adaptive conditioned responding. In L. Squire and N. Butters (Eds.) *Neuropsychology of Memory, 2nd Edition*, New York: Guilford, 1992, 510-518.

2. Moore, J.W. and Desmond, J.E. A cerebellar neural network implementation of a temporally adaptive conditioned response. In Gormezano, I. and Wasserman, E. A. (Eds.) *Learning and Memory: The Behavioral and Biological Substrates*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1992, 347-368.

3. Moore, J. W. A mechanism for timing conditioned responses. In F. Macar, V. Pouthas, and W. J. Friedman (Eds.) *Time, Action and Cognition*, Dordrecht, The Netherlands: Kluwer Academic Publishers, 1992, 229-238.

4. Moore, J.W. Computational Neuroscience. Review of Gluck, M.A. and Rummelhart, D.E. (Eds.) *Neuroscience and Connectionist Theory*, Hillsdale, N.J.: Lawrence Erlbaum Associates, 1990, 405 pp. *Contemporary Psychology*, 1993, 38: 137-139.

5. Hirl, M.J. and Moore, J.W. Single-unit activity in ventrolateral pons during conditioning of the rabbit nictitating membrane response. *Society of Neuroscience Abstracts*, 1992, 18: 337.

6. O'Connor, K.N. and Moore, J.W. Modulation of activity in the medial geniculate nucleus during auditory trace conditioning. *Society of Neuroscience Abstracts*, 1992, 18: 338.

7. Rosenfield, M.E. and Moore, J.W. Red nucleus projections to cerebellar cortex: Implications for classical eyeblink conditioning. *Society for Neuroscience*, 1993, 19: 1000.

8. Choi, J-S, Hirl, M.J. and Moore, J.W. Classical eyelid conditioning in rabbits with temporal uncertainty. *Society for Neuroscience Abstracts*, 1993, 19: 1000.

9. O'Connor, K.N., Allison, T.L., Rosenfield, M.E., and Moore, J.W. Modulation of neuronal activity in the medial geniculate during auditory trace conditioning. *Society for Neuroscience Abstracts*, 1993, 19: 1006.

10. Moore, J.W. Learning Theory and Mother Rabbit. Review of Hall, G. *Perceptual and Associative Learning*, Oxford: Clarendon Press, 1991, 300 pp. *American Journal of Psychology*, 1994, 107: 465-471.

11. Choi, J.S. and Moore, J.W. Asynchronous bilateral eyelid conditioning in rabbits. *Society for Neuroscience Abstracts*, 1994, in press.

V. Professional personnel

John W. Moore, Ph. D. (Psychology, Indiana) Principal Investigator.

Kevin O'Connor, Ph. D. (Psychology, Columbia University) Postdoctoral fellow. O'Connor joined the laboratory in July, 1990. He will be joining a group at the University of California-Davis to study auditory system information processing in monkeys, using single-unit recording skills acquired during his time of this project and its successor.

Marcy E. Rosenfield, B.S. (Zoology, UMass) Departmental Assistant. Rosenfield is a certified AALAS animal care technician.

Current Neuroscience and Behavior (NSB) graduate students

June-Seek Choi, M.A. (Physiological Psychology, Korea University). Choi joined my lab in Sept. 1992

Darlene Brunzell, B.A. (Psychology and Communication, University of Wisconsin). Brunzell joined my lab in August 1993.

VI. Interactions (John W. Moore)

1. Participant at the Winter Conference on Neurobiology of Learning and Memory, Park City, Utah, January 1992, 1993.

2. Attended New England Sequencing and Timing Conferences, held in Amherst, Mass, January, 1993 and March 1994. These conference were organized by colleague David Rosenbaum.

2. Attended the Reinforcement Learning Workshop held in conjunction with the Machine Learning 93 Conference, Amherst, MA, June, 1993

3. Attended Society for Neuroscience meeting in Washington DC, November 1993.

4. Attended the annual meeting of the Eastern Psychological Association, Providence, RI, April, 1994.

5. Reviewing and Related Activity: Consulting editor for Psychobiology and reviewed manuscripts for several journals, including Behavioural Brain Research, Psychological Review, Behavioral Neuroscience, Journal of Neuroscience, and several others.

6. Member of the Massachusetts Action Group, a regular interdisciplinary seminar organized by colleague David Rosenbaum. This group includes computer scientists and others interested in interdisciplinary approaches to perception and action.

7. Continuing interactive relationships with A G Barto and other colleagues working in Adaptive Networks: A H Klopf's group at AF Wright Avionics Lab, R S Sutton at GTE Labs, J C Houk and N A Schmajuk of Northwestern University, E J Kehoe of the University of New South Wales, and others.

VII. New Discoveries

Discoveries that might be designated as new were those stemming from experimental research.

Afferent Connections to Cerebellar Cortex (Larsell's HVI) in the Rabbit Demonstrated with WGA-HRP

ME Rosenfield and JW Moore

Figure 1. Reconstructed coronal sections showing placement of pipette (dots in white circles) and diffusion of label (black) for nine rabbits. The numbers at the base of the figure show the rostral (+) and caudal (-) distance in mm of each section from a plane passing through the accessory abducens nucleus. HVI = Larsell's hemispherical lobule VI, BC = brachium conjunctivum, LPN = lateral pontine nucleus, m5 = motor nucleus of the trigeminal nerve, 5 = trigeminal nerve, PSTN = principle sensory nucleus of the trigeminal nerve, IP = cerebellar nucleus interpositus, SO = superior olive, 7 = facial nerve, n7 = facial nucleus, D = dentate nucleus.

Figure 2. Reconstructed coronal sections at the level of the red nucleus with dots showing the location of retrogradely labelled cells in each of the nine cases. RN = red nucleus, 3 = oculomotor nerve

Figure 3. Reconstructed coronal sections at the level of the pontine nuclei with dots representing retrogradely labelled cells. BC = brachium conjunctivum, LPN = lateral pontine nucleus, MPN = medial pontine nucleus.

Figure 4. Reconstructed coronal sections at the level of spinal trigeminal nucleus pars oralis with dots representing retrogradely labelled cells. 6 = abducens nerve, 7 = facial nerve, SO = superior olive, SpO spinal oralis, LVN = lateral vestibular nucleus, MVN = medial vestibular nucleus, n7 = facial nucleus.

Figure 5. Reconstructed coronal sections at the level of the inferior olive with dots representing retrogradely labelled cells. SpO = spinal oralis, DAO = dorsal accessory olive, LRN = lateral reticular nucleus.

Figure 6. Summary diagram of brainstem and cerebellar circuits involved in rabbit eyeblink conditioning. The dashed lines represents the new pathways discovered in this experiment.

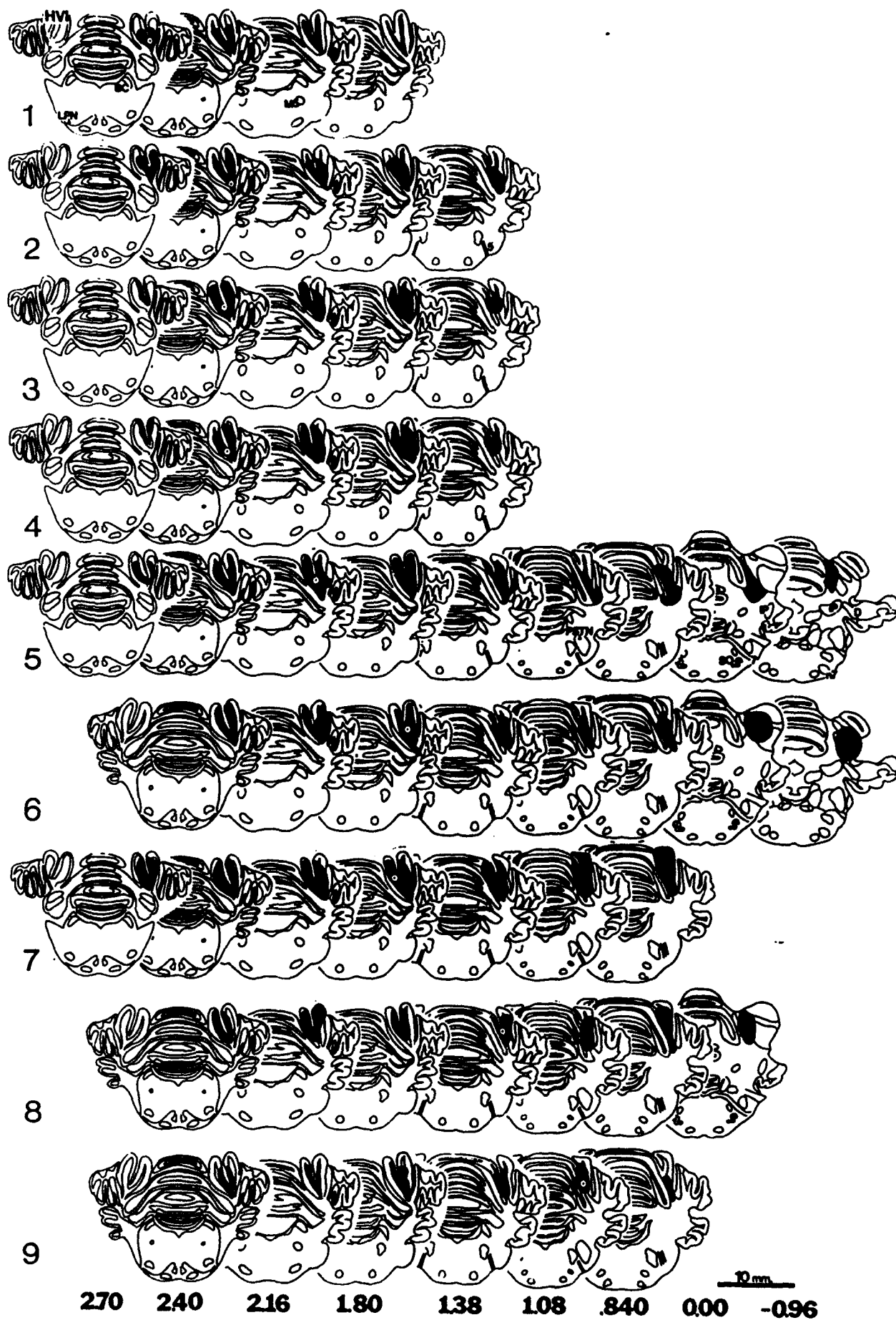


Fig. 1

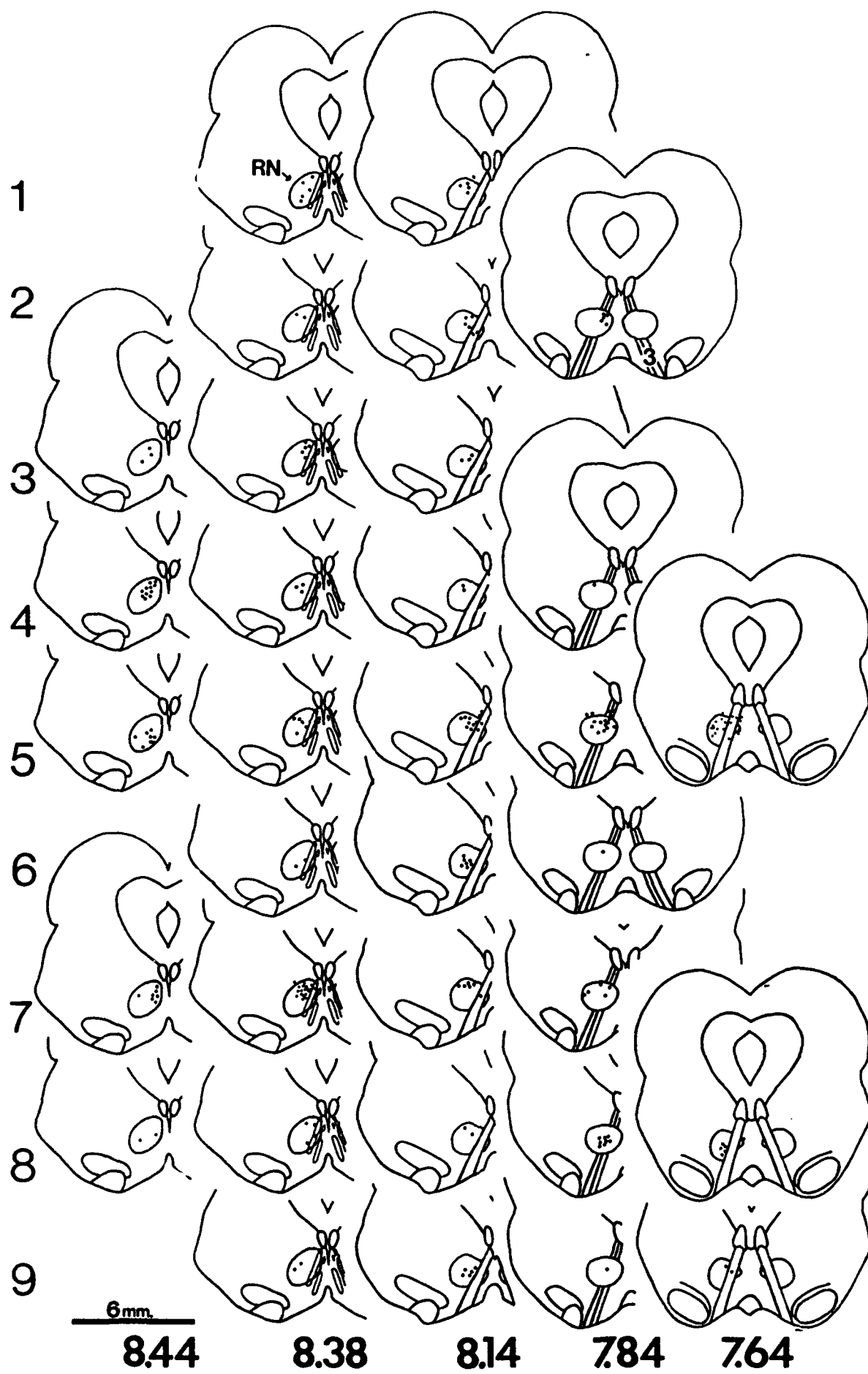
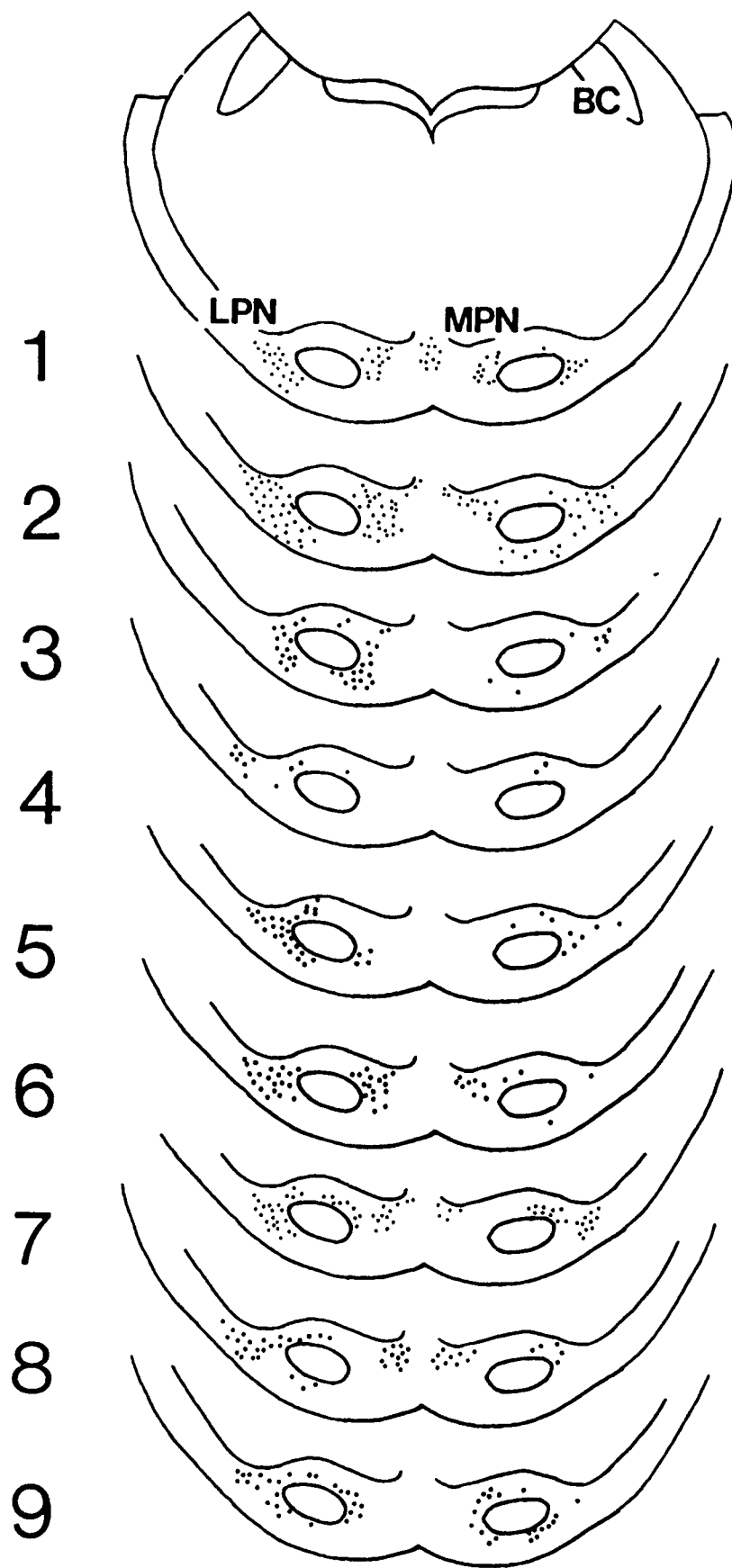


Fig. 2



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Fig. 3

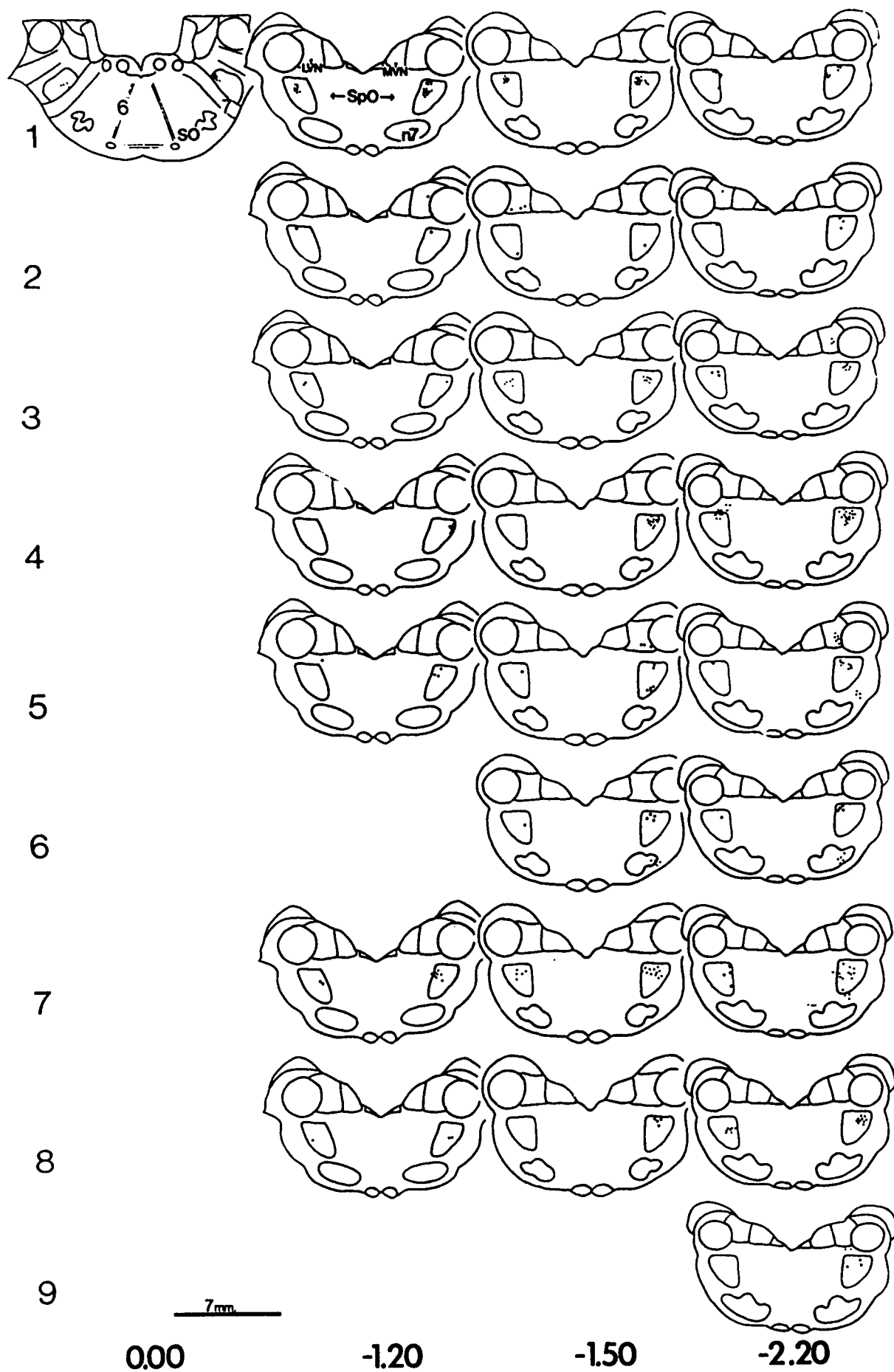


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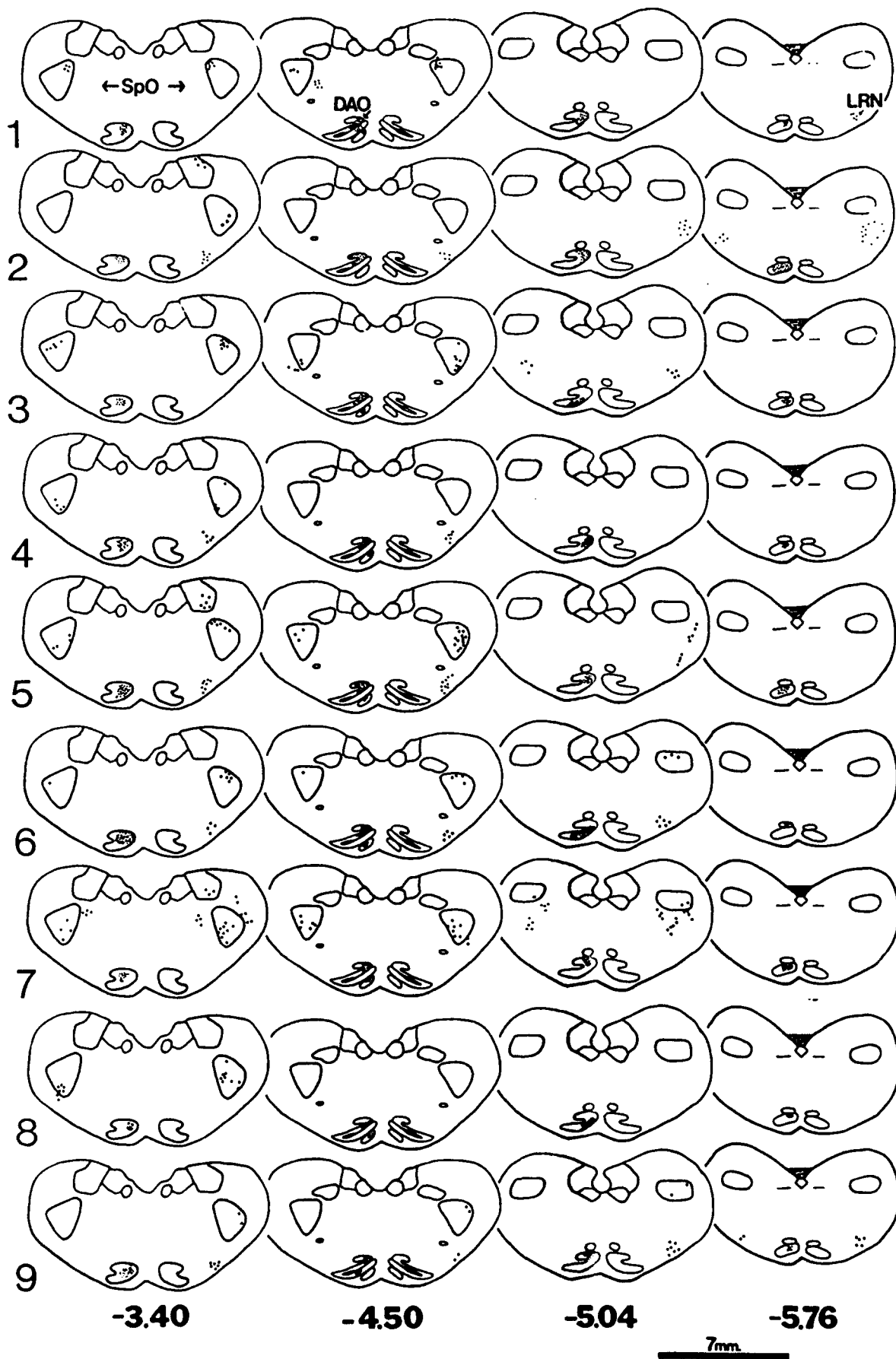


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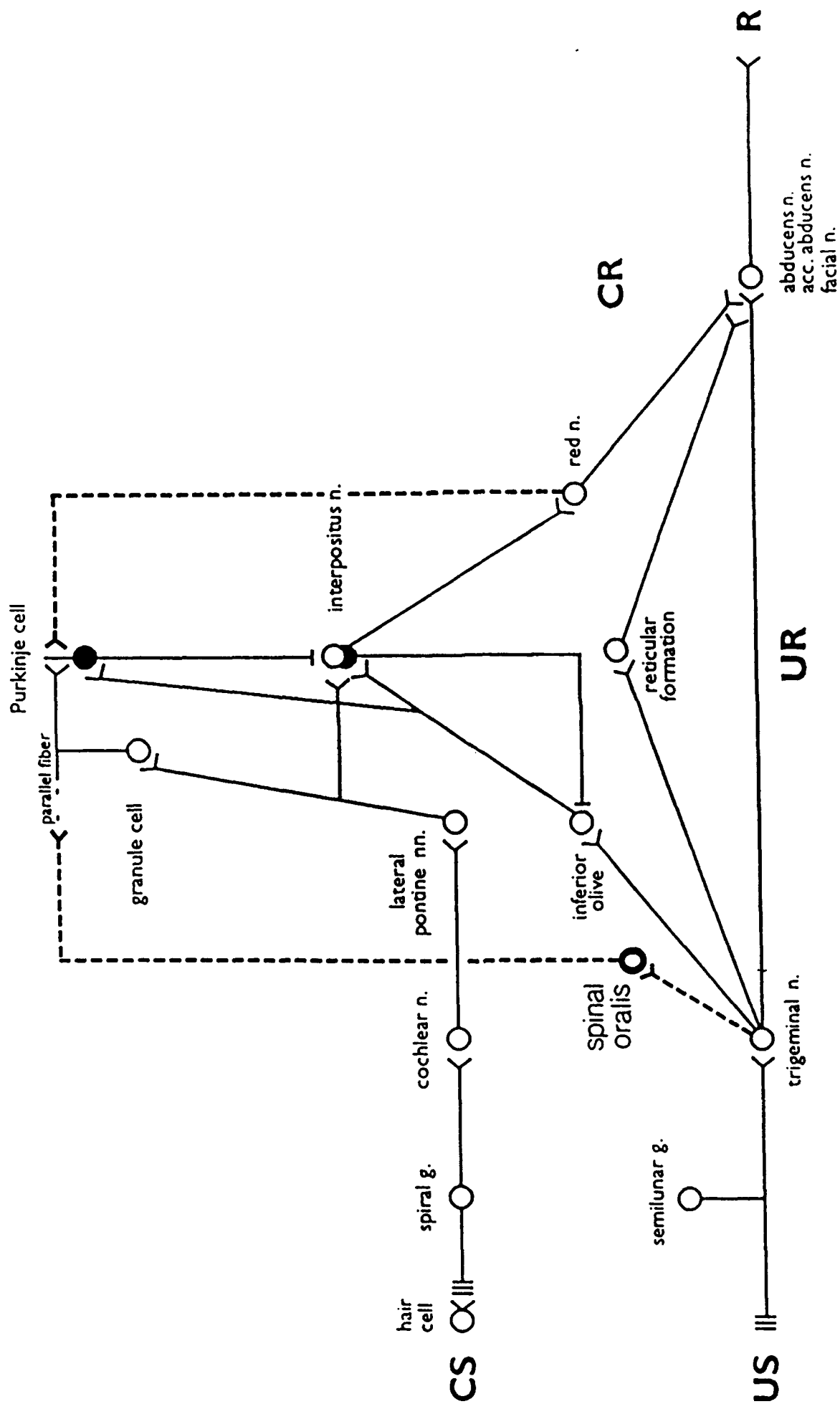


Fig. 6